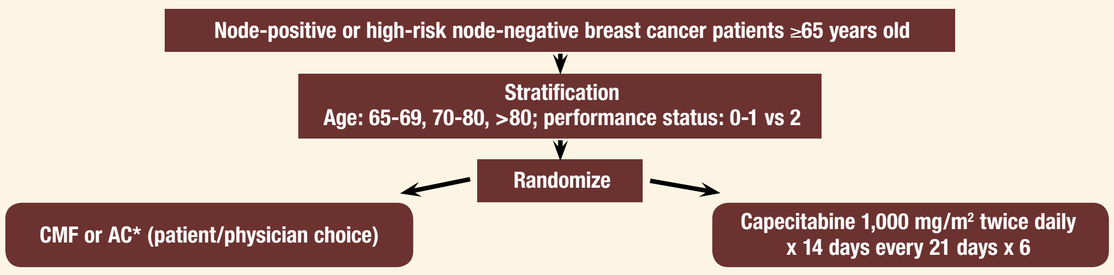
# CALGB-49907: Adjuvant Chemotherapy in Elderly Women

27TH ANNUAL
San Antonio Breast Cancer Symposium 13

**Relatively few randomized trials of adjuvant chemotherapy have included substantial numbers of elderly women, so a relative paucity of research data exists with regard to the risks and benefits of this intervention. This is particularly problematic in older women with estrogen receptor-negative tumors who will not receive endocrine therapy. Another common clinical dilemma is the elderly woman with an estrogen receptor-positive tumor for whom the incremental benefits and risks of chemotherapy in addition to endocrine treatment must be considered. An important related trial is being led by Dr Hyman Muss. CALGB-49907 randomly assigns elderly women with primary breast cancer to either the orally administered fluoropyrimidine prodrug capecitabine, or AC or CMF chemotherapy. In addition to evaluating disease-free and overall survival, a number of key quality-of-life endpoints are being evaluated.**

### CALGB-49907: ADJUVANT CMF OR AC VERSUS CAPECITABINE IN WOMEN 65 YEARS AND OLDER




* Patients whose LVEF is not within lower limits of normal must receive CMF, not AC. All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor for five years.

SOURCE: NCI Physician Data Query, October 2004.

### SUMMARY OF EFFICACY: SINGLE-AGENT CAPECITABINE VERSUS STANDARD CHEMOTHERAPY IN METASTATIC DISEASE

| Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF) as first-line therapy (n=93) | | |
|---|---|---|
| | **Capecitabine** | **CMF** |
| Response rate (95% CI) | 30% (19-43) | 16% (5-33) |
| Complete response | 5% | 0% |
| Median time to disease progression (95% CI) | 4.1 months (3.2-6.5) | 3.0 months (2.4-4.8) |
| Median survival | 19.6 months | 17.2 months |
| **Capecitabine versus paclitaxel as second-line therapy (n=41)** | | |
| | **Capecitabine** | **Paclitaxel** |
| Response rate (95% CI) | 36% (17-59) | 26% (9-51) |
| Complete response | 14% | 0% |
| Median time to progression (95% CI) | 3.0 months (1.4-6.6) | 3.1 months (2.5-6.5) |
| Median duration of response | 9.4 months | 9.4 months |

CI = confidence interval

DERIVED FROM: Biganzoli L et al. **Moving forward with capecitabine: A glimpse of the future.** *Oncologist* 2002;7(Suppl 6):29-35.

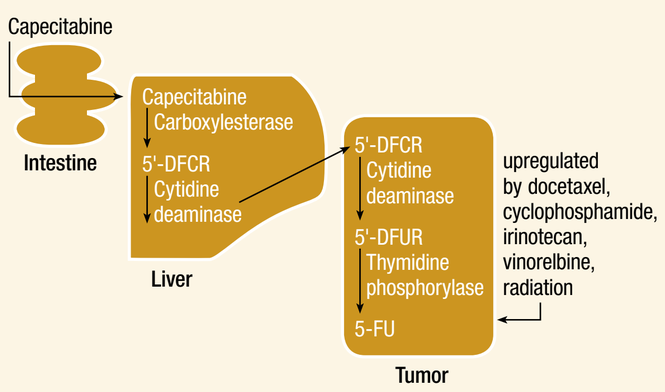
### PROPORTION OF ELDERLY PATIENTS (AGE ≥65) IN SWOG TRIALS AS COMPARED WITH THE PROPORTION OF ELDERLY PATIENTS WITH CANCER*

| Type of cancer | Percent of US cancer cases occurring in patients age ≥65 | Percent of enrolled patients age ≥65 |
|---|---|---|
| Breast | 49% | 9% |
| Brain | 44% | 19% |
| Colorectal | 72% | 40% |
| Leukemia | 63% | 27% |
| Lung | 66% | 39% |
| Myeloma | 70% | 25% |
| All types | 63% | 25% |

* The differences between the two groups were significant ($p < 0.001$) for all types of cancer listed.

SOURCE: Hutchins LF et al. **Underrepresentation of patients 65 years of age or older in cancer-treatment trials.** *N Engl J Med* 1999;341(27):2061-7.

### ENZYMATIC CONVERSION OF CAPECITABINE TO 5-FLUOROURACIL




### RATES OF OFFERING AND ACCEPTING CLINICAL TRIAL PARTICIPATION IN WOMEN

| Mean age (years) | Offered protocol | Consented when offered |
|---|---|---|
| 50.4 | 51% | 56% |
| 76.5 | 35% | 50% |

SOURCE: Kemeny M et al. **Barriers to clinical participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

### UNDER-REPRESENTATION OF ELDERLY WOMEN IN RECENT CALGB ADJUVANT TRIALS

| Trial regimens | Total accrued | Age 70 and older |
|---|---|---|
| CLB-8541<br>CAF in three different doses | 1,572 | 150 (10%) |
| CLB-9344<br>AC ± T | 3,170 | 182 (6%) |
| CLB-9741<br>A → T → C vs AC → T<br>in a q2wk vs q3wk schedule | 2,005 | 162 (8%) |

C = cyclophosphamide; A = doxorubicin; F = fluorouracil; T = paclitaxel

SOURCE: CALGB-49907 Protocol.

## SELECT PUBLICATIONS

Bouchardy C et al. **Undertreatment strongly decreases prognosis of breast cancer in elderly women.** *J Clin Oncol* 2003;21(19):3580-7.

Du X, Goodwin JS. **Patterns of use of chemotherapy for breast cancer in older women: Findings from Medicare claims data.** *J Clin Oncol* 2001;19(5):1455-61.

Extermann M et al. **What threshold for adjuvant therapy in older breast cancer patients?** *J Clin Oncol* 2000;18(8):1709-17.

Gagnon B et al. **Pattern of care at the end of life: Does age make a difference in what happens to women with breast cancer?** *J Clin Oncol* 2004;22(17):3458-65.

Kemeny MM et al. **Barriers to clinical trial participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

Mandelblatt JS et al. **Predictors of long-term outcomes in older breast cancer survivors: Perceptions versus patterns of care.** *J Clin Oncol* 2003;21(5):855-63.

O'Shaughnessy JA et al. **Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12(9):1247-54.

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72.



### *CALGB-49907: CAPECITABINE VERSUS CA/CMF IN THE ELDERLY*

CALGB-49907 is an Intergroup trial also available through the Cancer Trials Support Unit (CTSU) of the NCI that compares capecitabine with CA or CMF. Patients are randomly assigned to standard therapy — either CA or CMF — and the physician chooses which of these two regimens to use. The goal is to determine whether capecitabine is equally effective as standard adjuvant therapy.

Women eligible for this trial are 65 years and older with node-positive or high-risk, node-negative breast cancer. Women with ER-positive tumors can receive tamoxifen or anastrozole as their endocrine therapy.

Capecitabine is a reasonably safe drug, but patients need to be informed about side effects and toxicity. We are gathering excellent quality-of-life data and collecting adherence data with an electronic pill bottle. We are also evaluating some incredible laboratory science including genes that might tell us about toxicity, such as levels of thymidine phosphorylase, thymidylate synthase and dihydropyrimidine dehydrogenase (DPD). In addition, we'll be storing all the blocks for future work.

Although it's a little early for me to predict how to compare these regimens, I believe patients may perceive that capecitabine is a little easier to take because it is oral and not associated with alopecia.

*— Hyman B Muss, MD*

In addition to the more familiar ER, PR and HER2 markers, we are looking at some interesting predictive and prognostic markers and other biological markers. We are also examining how these drugs are metabolized in the elderly population. The data from the metastatic setting provided the rationale for selecting capecitabine for this trial. In addition to the convenience of an oral regimen, the trials comparing capecitabine to single-agent paclitaxel and to CMF demonstrated benefits from capecitabine in time to progression. However, capecitabine is not a benign drug, so we are closely monitoring patients.

*— Maria Theodoulu, MD*

### *CAPECITABINE IN ELDERLY PATIENTS*

We did a small, randomized Phase II trial comparing intravenous CMF and full-dose capecitabine as front-line therapy in elderly patients aged 55 years or older in the metastatic setting. The response rate with capecitabine was 30 percent compared to 16 percent with intravenous CMF.

In a randomized Phase II trial of patients pretreated with an anthracycline, comparing paclitaxel every three weeks to capecitabine, the response with capecitabine was 36 percent compared to 26 percent with paclitaxel. The confidence intervals were widely overlapping, so we couldn't conclude that capecitabine is superior.

What we can say from these two studies is that it's certainly unlikely that capecitabine is worse than CMF or paclitaxel. It's interesting how quickly capecitabine has moved to trials in the adjuvant setting. In women over age 65, the role of chemotherapy is unknown. For women over 70, in particular, the overview analysis includes so few patients in that age group that I think it's very reasonable to compare capecitabine to AC or CMF.

*— Joyce O'Shaughnessy, MD*

### *CALGB-49907: QUALITY-OF-LIFE SUBPROTOCOL*

Capecitabine is an obvious choice to study in the adjuvant setting. I'm most interested in Hyman Muss' Intergroup study comparing capecitabine versus AC or CMF in women over age 65. Based on the chemistry of capecitabine, it wouldn't surprise me if it proves to be equivalent in efficacy with a superior toxicity profile. In addition, it has the advantage of being an oral regimen.

US Oncology and MD Anderson each have adjuvant studies evaluating the combination of capecitabine and docetaxel, but these trials are not mature and it will be some time before we know the results.

*— Daniel R Budman, MD*